II. REMARKS

Claims 1 to 4, 7 to 14, 18 to 22, and 24 to 26 are pending.

The objection to the specification and corresponding rejection of claims 1-4, 7-14, 18-22, and 24-26 under 35 U.S.C. § 112, first paragraph, as allegedly lacking enablement are respectfully traversed.

It is maintained in the Office action that, while the specification enables detection of mutant p53 in tissues prior to histological evidence of neoplastic pathology, it is unpredictable whether the recited mutant target nucleic acids (e.g., APC, DCC, NF1, NF2, VHL, and WT-1) could similarly be detected in tumor margins and lymph nodes not exhibiting morphologic characteristics indicative of neoplastic pathology. In particular, it is stated in the Office Action that the art suggests that only neoplastic nucleic acids that are mutated early in the process of carcinogenesis would be detectable prior to the development of histological evidence of a cancer (citing to Nees *et al.* as indicating that mutation of p53 is likely an early event in head and neck carcinogenesis). As such, it is alleged that, absent evidence that mutations of the recited target nucleic acids occur sufficiently early in the development of cancer, one skilled in the art would not have expected the target mutant nucleic acids, as claimed, to be detectable before histological evidence of cancer is evident.

Applicants point out, however, that the claims are directed to methods of detecting the presence of neoplastic cells of a primary neoplasm, in a histologically normal specimen from a site distant from the primary neoplasm, by detecting in the specimen the presence of a mutant target nucleic acid that is present in the primary neoplasm. The present methods are based on the finding that a mutant nucleic acid that is associated with a primary tumor can be detected in adjacent surgical margins and more distant tissues such as lymph nodes that appear histologically

normal (see, e.g., page 4, lines 2-6). As such, the claims require that the skilled artisan, practicing the methods, have knowledge of one or more mutant target nucleic acids (APC, DCC, NF1, NF2, RET, VHL, and/or WT-1) in the primary neoplasm (see, e.g., claim 1, which recites that "the mutant nucleic acid is present in the primary neoplasm and the specimen", and requires "detecting the presence of the mutant target nucleic acid" in a specimen, which is "external to the primary neoplasm and [ ] does not exhibit morphological characteristics indicative of neoplastic pathology").

It is stated in the Office Action that the specification fails to disclose that target nucleic acids, as recited in the claims, have mutations at a sufficiently early stage of cancer development such that they can be detected before cells having the mutant nucleotide sequences appear histologically normal. In support of this position, Nees *et al.* is cited as teaching that different p53 mutations were present in different tumor-distant biopsies from the same patient, and that the presence of multiple developing tumors that were polyclonal in nature indicates that p53 mutations occur early in carcinogenesis (see, e.g., page 4189, last sentence of the Abstract). Applicants submit, however, that the teaching of Nees *et al.* is not particularly relevant to the claimed methods, which require detecting, in a specimen, a mutant target nucleic acid "that is present in the primary neoplasm." More specifically, the claimed methods are not directed to identifying neoplastic cells at an early stage of transformation, before the transformed cells appear histologically abnormal, but, instead, provide a means to detect neoplastic cells that have migrated (e.g., by invasion or metastasis) from the primary neoplasm, but are not detectable using histologic methods. As disclosed in the specification, such a normal histological appearance can be due, for example, to a low number of neoplastic cells relative to normal cells in the specimen (e.g., one neoplastic cell in 10,000 normal cells; see, e.g., page 4, lines 3-15). Further, the skilled artisan would have known that that mutations in APC, DCC, NF1, NF2, RET, VHL, and WT-1 genes, like p53 mutations, can be present in and contribute to the etiology of a neoplasm (see, also, Table 1, page 11). As such, it is submitted that one skilled in the art,

viewing the subject application, and knowing that a primary neoplasm of a subject contains a mutant nucleic acid (e.g., mutant APC gene), would have known how to detect the mutant target nucleic acid in specimen that appears histologically normal (e.g., tumor surgical margin) and, therefore, how to practice the claimed methods.

In summary, the claims are directed to a method of detecting, in a histologically normal tissue specimen, a mutant target nucleic acid (e.g., APC, DCC) that is present in a primary neoplasm. The specification discloses that such a histologically normal tissue specimen can be a tumor margin or lymph node, which contains, for example, one neoplastic cell in 10,000 normal cells, and discloses that mutations of APC, DCC, NF1, NF2, RET, VHL, and WT-1 genes occur in primary neoplasms. As such, it is submitted that the skilled artisan reasonably would have predicted that the claimed methods could identify, for example, the presence of tumor cell invasion and/or metastatic cancer in otherwise normal appearing tissue, and would have known how to practice the claimed methods without undue experimentation. Accordingly, it is respectfully requested that the objection to the specification be withdrawn, and that the corresponding rejection of the claims under 35 U.S.C. § 112, first paragraph, be removed.

In view of the above remarks, it is submitted that the claims are in condition for allowance, and a notice to that effect is respectfully requested. The Examiner is invited to contact Applicant's undersigned representative if there are any questions relating to the subject application.

The Commissioner is hereby authorized to charge any fees that may be necessary in connection with the filing of this Communication, or credit any overpayment, to Deposit Account No. 07-1896.

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Respectfully submitted,

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Richard J. Imbra
Registration No. 37,643
Telephone: (858) 677-1496
Facsimile: (858) 677-1465

DLA PIPER RUDNICK GRAY CARY US LLP
4365 Executive Drive, Suite 1100
San Diego, CA 92121-2133
USPTO CUSTOMER NO. 28213